REMARKS

Claims 2-17, 19, 20, 22, 24-27, 29-33, 35-38, 40-47, 49-54, and 68-88 are pending and under consideration. With this Amendment, Claims 50-52 are being amended. Thus, after entry of this Amendment, Claims 2-17, 19, 20, 22, 24-27, 29-33, 35-38, 40-47, 49-54, and 68-88 are pending and under consideration. The amendments of the claims and the various rejections raised in the Office Action are discussed in more detail, below.

The Amendments of the Claims

Claims 50-52 are amended to correct an obvious typographical error. No new matter is added by virtue of the amendments.

Rejection Under 35 U.S.C. § 103(a)

Claims 2, 3, 8, 10, 14-17, 19, 22, 24, 30, 33, 35-38, 40-47, 49-54, 68-77, and 84-85 stand rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,207,752 to Sorenson *et al.* ("Sorenson *et al.*") in view of Palmeri *et al.* and U.S. Patent No. 6,436,091 to Harper *et al.* ("Harper *et al.*") for reasons of record in the Office Actions dated March 18, 2004, December 15, 2005, and September 28, 2005. Applicant traverses the rejection.

Applicant maintains that the cited art does not support an obviousness rejection. Section 103(a) precludes the grant of a patent only if "differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains." 37 U.S.C. § 103(a). The Office bears the initial burden of establishing a case of *prima facie* obviousness. *In re Bell*, 26 USPQ2d 1529, 1530 (Fed. Cir. 1993); *In re Fine*, 5 USPQ2d 1956, 1958 (Fed. Cir. 1998); MPEP § 2142. If the Office does not establish a *prima facie* case, the Applicant is under no obligation to submit evidence of nonobviousness, and the rejection must be withdrawn. *Id.*

To establish a *prima facie* case, three criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation that the modification or combination would be successful. Third, the prior art reference (or references when combined) must teach all the limitations of the rejected claims. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must

both be found in the prior art, and not based upon Applicant's disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991), *citing In re Dow*, 5 USPQ2d 1529 (Fed. Cir. 1988); MPEP § 2142.

The claimed invention is drawn to a method comprising determining a well-tolerated, therapeutic pharmacokinetic profile for interferon therapy in a subject using one or more interferons formulated for short-term delivery and administering to the subject using at least one internally presented, not externally programmable pump one or more interferons formulated for long-term delivery in which the interferons are released from the pump at a rate that substantially achieves the pharmacokinetic profile of the interferon formulated for short-term delivery during the long-term delivery.

In contrast to the claimed invention, the primary reference relied upon by the Office, Sorenson *et al.*, discloses a "method and apparatus for iontophoretic drug delivery wherein the initial high current level is maintained for a predetermined time to provide that drug concentration in the bloodstream reaches a temporary *peak value* and thereafter *subsides* to a *maintenance level*." (column 2, lines 10-15, *emphasis added*). Thus, in Sorenson *et al.*, the maintenance level can not achieve the peak value because the maintenance level is reached by allowing the peak value to subside. Therefore, in at least this respect, Sorenson *et al.* teach away from the claimed invention in which the long-term formulation achieves the pharmacokinetic profile of the short-term formulation.

The Office has not taken issue with Applicant's interpretation of Sorenson *et al.* However, in maintaining the rejection, the Office states that the Sorenson *et al.* reference was included in the rejection for another purpose:

> Applicants argue that Sorenson et al. provide a subject with an initial peak level of drug concentration that is followed by lower maintenance levels (see page 16 of the response filed 3/28/06). Thus, the initial drug concentration of Sorenson et al. is reduced and is not substantially achieved over the period of long-term delivery. Contrary to Applicants assertions, as indicated previously (18 March 2004), the Sorenson reference was included [in the rejection] to teach a device and methods for introducing a therapeutic agent for a first interval (short term), then introducing the same agent at a second level for the purpose of maintenance (column 2, lines 10-21). Interferons are specifically taught at column 7, line 1.

In view of the Office's statement that the Sorenson *et al.* was included in the rejection for another purpose, Applicant respectfully asserts that the Office is not viewing Sorenson *et al.* as a whole and, in addition, is using impermissible hindsight analysis to formulate its rejection. When applying 35 U.S.C. § 103 the references must be considered as a whole and viewed without the benefit of hindsight vision afforded by the claimed invention. *Hodash v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ

182, 187 n.5 (Fed. Cir. 1986); MPEP § 2141. Applicant respectfully asserts that the Office's statement (quoted above) that Sorenson *et al.* was included in the rejection to only provide specific teachings indicates that the Office is not considering aspects of Sorenson *et al.* that do not support its theory unpatentability. This practice is improper. All aspects of Sorenson *et al.* and the other references, including those that teach away from the claimed invention or do not support the rejection must be considered. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984); MPEP § 2141.03. It is inappropriate for the office to select parts of a reference out of context of the teachings of the entire reference to support a rejection. As summarized above, Sorenson *et al.* teach a peak value that subsides to a maintenance level and therefore teach away from the claimed invention. Thus, the Office's primary reference, Sorenson *et al.*, does not support a conclusion of obviousness.

The Office contends that Palmeri *et al.* "was included [in the rejection] to teach the administration of different levels of interferon to achieve an optimal dosage." Applicant respectfully asserts that this is a mischaracterization of Palmeri *et al.* Palmeri *et al.* describe a study to determine a *maximally tolerated dose* of recombinant alpha interferon in combination with 5-fluorouracil ("5FU"). (Abstract, *emphasis added*). The Office contends that the maximally tolerated dose of Palmeri *et al.* is an optimal dose but Palmeri *et al.* do not support the Office's position. Palmeri *et al.* state that the "combination is now *ready to be tested* in larger phase II-III studies *in order to evaluate its therapeutic activity.*" (*see* Discussion, *emphasis added*). Therefore, contrary to the Office's position, Palmeri *et al.* do not suggest that the maximally tolerated dose is therapeutic or is in any way optimal.

The Office also contends that the motivation to combine the references can be found in Palmeri *et al.* because Palmeri *et al.* disclose a problem that can be solved by the method of Sorenson *et al.* and Harper *et al.* The Office contends that Palmeri *et al.* teach the problem of "long-term administration of optimized dozes of interferon for the treatment of colorectal cancer." Applicant respectfully disagrees. As stated above, Palmeri *et al.* do not disclose optimized doses. Furthermore, the problem stated by Palmeri *et al.* is increasing the therapeutic activity of 5FU (*see* Introduction). Palmeri *et al.* do not state or suggest that long-term delivery is a problem in the treatment of colorectal cancer. Palmeri *et al.* disclose a study to determine a maximally tolerated dose of subcutaneously administered recombinant alpha interferon ("ralFN-2a") which Palmeri *et al.* identify on page 330. Therefore, the Office makes an unsupported conclusion regarding the problem of Palmeri *et al.* and its resolution by the application of Sorenson *et al.* and Harper *et al.*

Applicant also respectfully asserts that the Office's admission that Palmeri *et al.* was cited for specific teachings indicates that the Office has not viewed Palmeri *et al.* as a whole and is using impermissible hindsight analysis to formulate its rejection.

The third reference, Harper *et al.*, disclose a pump for delivering a pharmaceutical agent to a patient but Harper *et al.* do not cure the deficiencies of Sorenson *et al.* or Palmeri et. al. summarized above.

Thus, Applicant respectfully asserts the references either alone or in combination do not teach or suggest all the claim limitations and therefore there can be no motivation to combine the references to arrive at the claimed invention. Applicant respectfully asserts that the Office has not viewed the references as a whole and has used impermissible hindsight analysis to combine the references to arrive at the claimed invention. Using Applicant's disclosure as a guide, the Office identifies aspects of the references it believes to be at least suggestive of the claimed invention and has used unsupported assertions regarding their interpretation and combination to support its conclusion of obviousness.

Therefore, Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Claims 3-7, 12, 13, 19, 20, 22, 24, 25-27, 29, 32, 33, 68, 74, 78-83 and 86-88 stand rejected under 35 U.S.C. § 103(a) as being obvious over Sorenson *et al.* in view of Palmeri *et al.* and Harper *et al.* in further view of Johnson *et al.* Applicant traverses the rejection.

Applicant respectfully asserts that the arguments put forth above regarding Sorenson *et al.*, Palmeri *et al.*, and Harper *et al.* apply in traversing the present rejection. Johnson *et al.*, who disclose various types of interferons and their use in the treatment of disease, do not cure the deficiencies of Sorenson *et al.*, Palmeri *et al.*, and Harper *et al.* Therefore, Applicant respectfully submits that the rejection under 35 U.S.C. § 103(a) is improper and respectfully requests that it be withdrawn.

Claims 2, 11, 22, 31, 68, and 74 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Sorenson *et al.* in view of Palmeri *et al.*, Harper *et al.*, and Johnson *et al.* in further view of U.S. Patent No. 4,837,079 to Kwan ("Kwan").

Applicant respectfully asserts that the arguments put forth above regarding Sorenson *et al.*, Palmeri *et al.* Harper *et al.*, and Johnson *et al.* apply in traversing the present rejection. Kwan discloses interferon/thimerosol mixtures and therefore can not cure the deficiencies of Palmeri *et al.* Harper *et al.*, and Johnson *et al.* Therefore, Applicant respectfully submits that the rejection under 35 U.S.C. § 103(a) is improper and respectfully requests that it be withdrawn.

Claims 2-17, 19, 20, 22, 24-27, 29-33, 35-38, 40-47, 49-54, and 68-88 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Sorenson *et al.* in view of Palmeri *et al.*, U.S. Patent No. 5,728,396 to Peery *et al.* ("Peery *et al.*"), and Johnson *et al.* in further view of Kwan.

Applicant respectfully asserts that the arguments put forth above regarding Sorenson *et al.*, Palmeri *et al.*, Harper *et al.*, Johnson *et al.*, and Kwan apply in traversing the present rejection. Peery *et al.* disclose the sustained delivery of leuprolide using an implantable system and therefore can not cure the deficiencies of Palmeri *et al.*, Harper *et al.*, Johnson *et al.* and Kawn. Therefore, Applicant respectfully submits that the rejection under 35 U.S.C. § 103(a) is improper and respectfully requests that it be withdrawn.

Rejection Under 35 U.S.C. § 112, ¶ 1

Claims 68 and 74 stand rejected under 35 U.S.C. § 112, ¶ 1, as failing to comply with the written description requirement. The Office contends the term "internally presented, not externally programmable pump" has no support in the specification. Applicant respectfully traverses the rejection.

On page 19, the specification describes the DUROS® system, which is known in the art to be an internally presented, not externally programmable pump. Therefore, Applicant respectfully requests the rejection be withdrawn.

Conclusion

The claims are believed to satisfy all of the criteria for patentability and are in condition for allowance. An early indication of same is therefore kindly requested.

Applicant hereby requests a one-month extension thereby extending the period for response to October 9, 2006. The Commissioner is authorized to charge any fees that may be required, or credit any overpayment, to Dechert LLP Deposit Account No. 50-2778 **(Order No. 375608-004US (360890))**.

Respectfully submitted,

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